Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study

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Summary

Background Hormonal contraceptives are used widely but their effects on HIV-1 risk are unclear. We aimed to assess the association between hormonal contraceptive use and risk of HIV-1 acquisition by women and HIV-1 transmission from HIV-1-infected women to their male partners.

Methods In this prospective study, we followed up 3790 heterosexual HIV-1-serodiscordant couples participating in two longitudinal studies of HIV-1 incidence in seven African countries. Among injectable and oral hormonal contraceptive users and non-users, we compared rates of HIV-1 acquisition by women and HIV-1 transmission from women to men. The primary outcome measure was HIV-1 seroconversion. We used Cox proportional hazards regression and marginal structural modelling to assess the effect of contraceptive use on HIV-1 risk.

Findings Among 1314 couples in which the HIV-1-seronegative partner was female (median follow-up 18·0 [IQR 12·6–24·2] months), rates of HIV-1 acquisition were 6·61 per 100 person-years in women who used hormonal contraception and 3·78 per 100 person-years in those who did not (adjusted hazard ratio 1·98, 95% CI 1·06–3·68, p=0·03). Among 2476 couples in which the HIV-1-seronegative partner was male (median follow-up 18·7 [IQR 12·8–24·2] months), rates of HIV-1 transmission from women to men were 2·61 per 100 person-years in couples in which women used hormonal contraception and 1·51 per 100 person-years in couples in which women did not use hormonal contraception (adjusted hazard ratio 1·97, 95% CI 1·12–3·45, p=0·02). Marginal structural model analyses generated much the same results to the Cox proportional hazards regression.

Interpretation Women should be counselled about potentially increased risk of HIV-1 acquisition and transmission with hormonal contraception, especially injectable methods, and about the importance of dual protection with condoms to decrease HIV-1 risk. Non-hormonal or low-dose hormonal contraceptive methods should be considered for women with or at-risk for HIV-1.

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Introduction

Safe and effective family planning services are central to initiatives to reduce unintended pregnancies, promote economic development, and improve the health of women and children worldwide. Among women with and at-risk for HIV-1, the prevention of unintended pregnancy is a key component of strategies to reduce vertical HIV-1 transmission.[1,2]

Hormonal contraceptive methods, including daily oral pills and long-acting injectables, are used by more than 140 million women worldwide.[3] During the past two decades, epidemiological and laboratory studies have suggested that hormonal contraception could alter the risk of HIV-1 acquisition in women.[4–8] However, results have been inconsistent.[9] Only one study has addressed the effect of hormonal contraception and risk of HIV-1 transmission from women to men.[10] Increased risk related to hormonal contraceptive use would be of importance to global public health because of the large number of women using such methods. WHO has called for high-quality studies to assess the potential role of hormonal contraception in increased HIV-1 risk.[11,12] We aimed to assess the association between hormonal contraceptive use and risk of HIV-1 acquisition by women and HIV-1 transmission from HIV-1-infected women to their male partners.

Methods

Study design and participants

From 2004–10, we did two prospective studies of HIV-1 incidence in African HIV-1-serodiscordant couples (ie, one partner with HIV-1 infection and one partner without). The Partners in Prevention HSV/HIV Transmission Study was a randomised, placebo-controlled, trial of daily acyclovir herpes simplex virus type 2 (HSV-2) suppressive therapy given to 3408 people infected with HIV-1 and HSV-2 as an intervention to reduce HIV-1 transmission to their heterosexual HIV-1-seronegative partners (Clinicaltrials.gov #NCT00194519); acyclovir did not significantly reduce HIV-1 transmission.[13] Couples were from seven countries in east and southern Africa (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia) and were followed for up to 24 months. In a parallel study at two of the clinical trial sites (Kampala, Uganda, and Soweto, South Africa), we enrolled an additional 485 HIV-1 serodiscordant

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couples into an observational study of immune correlates of HIV-1 protection and followed them for up to 12 months. For both studies, eligible participants were aged 18 years or older and sexually active, HIV-1-seropositive partners had no history of AIDS-defining disorders and were not using antiretroviral therapy (ART), the HIV-1-seropositive partners in the clinical trial had CD4 counts of 250 cells per μL or higher, were seropositive for HSV-2, had no known history of adverse reactions to acyclovir, and were not pregnant. Couples were recruited through study-initiated community outreach activities and referrals from HIV-1 testing and care centres, antenatal clinics, and non-governmental organisations.[14] The main reasons couples did not enrol were that they did not meet the CD4 count, HSV-2, pregnancy, or sexual activity eligibility criteria.[15]

HIV-1-uninfected partners were seen quarterly for HIV-1 serological testing. For HIV-1-infected partners, CD4 counts were measured every 6 months, and participants eligible for ART initiation during follow-up were referred to local HIV-1 care clinics. All participants received comprehensive HIV-1-prevention services, including individual and couples counselling, free condoms, and treatment of sexually transmitted infections. Contraceptives were offered by referral or on-site. Differences in contraceptive use occurred between sites.[16,17]

We excluded enrolled patients who were subsequently reported to not have HSV-2 or HIV-1 infection and couples for whom the HIV-1 uninfected participant did not complete any follow-up visits for assessment of HIV-1 seroconversion. We also censored visits for couples for whom the HIV-1 infected partner started ART, because such treatment eliminated HIV-1 risk in the study population.[18] The protocols were approved by institutional review boards at the University of Washington and collaborating institutions at each study site. Participants provided written informed consent.

Procedures

Rapid HIV-1 antibody tests were used for HIV-1 serological testing and positive results were confirmed by ELISA.[13] For HIV-1 seroconverters, analysis of HIV-1 *env* and *gag* sequences from both members of a couple was used to establish whether transmission was linked within the partnership.[19] Nucleic-acid-amplification testing for bacterial sexually transmitted infections (STIs) was done on samples collected from both partners at study enrolment.[15] All participants were tested for HSV-2 with HerpeSelect-2 EIA (Focus Technologies, Cypress, CA, USA) or by HSV-specific western blot.[20] CD4 quantification was done with standard flow cytometry. Plasma HIV-1 RNA concentrations were quantified from a sample collected at study enrolment and 6 months later with the COBAS TaqMan real-time HIV-1 RNA assay, version 1.0 (Roche Diagnostics, Indianapolis, IN, USA). Concentrations of endocervical HIV-1 were quantified with the COBAS assay of swab samples collected 6 months after enrolment from HIV-1- infected women in the clinical trial cohort, as previously detailed.[21] The lower quantification limit for HIV-1 RNA testing was 240 copies.

At each quarterly study visit, women were asked about their current contraceptive method with a standard questionnaire. Women were classified as exposed to hormonal contraception for each quarterly period if they reported hormonal use at the quarterly visit. Contraceptive use was analysed as a time-dependent exposure, with women assumed to have used the same method during the 3 months that elapsed between study visits. Analyses were done for exposure to any hormonal contraception and then separately for injectable and oral contraception; the comparison group was women not using hormonal contraception, which included women who had had a hysterectomy or tubal ligation, used condoms only, or used no contraception. Visits at which women reported use of implantable hormonal methods or an intrauterine device were rare (<2% of visits) and therefore excluded. Many women reported condom use, either with or without another method for contraception; condom use was thus included in analyses as a potential confounder. HIV-1-uninfected men were classified as exposed to hormonal contraception if their HIV-1-infected female partner reported using an injectable or oral method at her corresponding study visit. For 4% of male follow-up time, missing contraceptive data from their female partners were imputed to be the method consistently reported at adjacent study visits; data were not imputed if methods during adjacent periods were inconsistent.

Statistical analysis

The primary outcome measure was HIV-1 seroconversion. We did separate analyses of the association of hormonal contraception with HIV-1 acquisition by women (male-to-female transmission) and HIV-1 transmission from women to men (female-to-male transmission). For female-to-male transmission, only genetically linked seroconversions were included as outcomes to minimise misclassification of HIV-1 transmissions from outside partners with unknown hormonal contraceptive use, and follow-up time was censored for those men at the time they acquired HIV-1 from a partner other than the HIV-1-infected partner with whom they enrolled.

We compared participant characteristics during periods of hormonal contraceptive use and non-use with generalised estimating equations. To assess the effect of contraceptive method on HIV-1 risk, we used time-dependent Cox proportional hazards regression with robust standard errors to account for within subject correlation with repeated measurements.[22] Models were adjusted for variables that had confounded the contraception–HIV-1-risk relation in previous analyses[7,8]—age and time-dependent pregnancy and any sex without condoms—and plasma HIV-1 concentrations in HIV-1-infected partners, a strong predictor of HIV-1

transmission.[23] We also assessed several additional variables for potential confounding: region (east Africa *vs* southern Africa), marital status of couples and the number of children they had together, HSV-2 status of the HIV-1-uninfected partner, circumcision status of the male partner, and STI in either partner, all recorded at study enrolment, and time-dependent measures of sexual frequency (with and without condoms), sex with additional partners, CD4 count of the HIV-1-infected partner, and genital-ulcer disease in either partner. None of these additional variables substantially (>10%) changed the effect estimates and thus they were not included in the final multivariate models. For analysis of HIV-1 acquisition by women, we tested for effect modification by baseline HSV-2 status and age with a likelihood-ratio test, because previous results have shown that the hormonal contraception–HIV-1-risk relation was stronger for women who were HSV-2 seronegative or who were aged less than 25 years.[24]

We repeated our analyses with marginal structural modelling, a technique to adjust for time-dependent confounding.[25,26] We computed stabilised-inverse-probability weights with logistic regression to predict the probability of hormonal contraceptive use at each visit (by concentrations of plasma HIV-1, age, region, and number of children), as described by Cole and colleagues;[27] the weights adjusted for time-dependent measures of pregnancy and unprotected sex. Weights for the effect of any hormonal contraception on HIV-1 risk (mean 1·00, range 0·82–1·34) were computed separately from the weights to assess the separate effects of injectable and oral contraception on HIV-1 risk (mean 1·07, range 0·19–4·56). These weights were then used in a pooled logistic-regression model of hormonal contraception versus HIV-1 risk.

Finally, we assessed the prevalence and quantity of genital HIV-1 RNA in women using hormonal contraception versus those who did not by logistic and linear regression. All analyses were done with SAS 9.2.

	Analysis of HIV-1 acquisition by women (N=1314 couples)		Analysis of HIV-1 transmission from women to men (N=2476 couples)	
	HIV-1-uninfected women	HIV-1-infected men	HIV-1-uninfected men	HIV-1-infected women
Demographic characteristics				
Age, years	30·2 (25·0–37·2)	37·0 (31·8–44·1)	35·0 (29·5–42·0)	29·9 (25·1–34·6)
Education, years	8·0 (6·0–10·0)	8·0 (6·0–11·0)	9·0 (7·0–12·0)	8·0 (6·0–11·0)
Couple characteristics*				
Married	1081 (82·3%)	..	1846 (74·6%)	..
Partnership duration, years	6·5 (2·7–13·4)	..	4·9 (2·1–9·4)	..
Number of children	2·0 (1·0–4·0)	..	2·0 (1·0–4·0)	..
Number of children with study partner	2·0 (0·0–3·0)	..	1·0 (0·0–2·0)	..
Sexual behaviour, month before enrolment				
Number of sex acts with study partner	3·0 (2·0–6·0)	..	4·0 (2·0–8·0)	..
Any unprotected sex with study partner	312 (23·7%)	..	727 (29·4%)	..
Any sex with an outside partner	8 (1·0%)	98 (7·5%)	119/1293 (9·2%)	34 (1·4%)
Medical characteristics				
Sexually transmitted infection†	160 (14·5%)	85 (6·6%)	230/2411 (9·5%)	429/2231 (19·2%)
HSV-2 seropositive	1088/1283 (84·8%)	1249/1280 (97·6%)	1441/2393 (60·2%)	2440 (99·0%)
Circumcised (men)	..	427 (32·5%)	1332 (53·8)	..
Ever pregnant during study (women)	390 (29·7%)	..	..	571 (23·1%)
HIV-1 characteristics				
Plasma HIV-1 RNA, (log_{10} copies per mL) at enrolment	..	4·37 (3·71–4·94)	..	3·97 (3·24–4·56)
CD4 count (cells per μL) at enrolment	..	417 (323–562)	..	478 (348–663)
Ever used ART during study	..	173 (13·3%)	..	235 (9·6%)
Contraceptive use (women)				
Any hormonal contraceptive use at enrolment	194 (14·8%)	..	..	430 (17·4%)
Any injectable use at enrolment	142 (10·8%)	..	..	335 (13·5%)
Any oral use at enrolment	52 (4·0%)	..	..	95 (3·8%)
Any hormonal contraceptive use during follow up	275 (20·9%)	..	..	815 (32·9%)
Any injectable contraceptive use during follow up	208 (15·8%)	..	..	656 (26·5%)
Any oral contraceptive use during follow up	87 (6·6%)	..	..	219 (8·8%)

Data are number (%), n/N (%), or median (IQR). HSV-2=herpes simplex virus type-2. ART=antiretroviral therapy. *Data shown in the uninfected group apply to couples. †*Neisseria gonorrhoeae, Chlamydia trachomatis,* or *Trichomoas vaginalis*; 678 (75%) of 904 participants with a sexually transmitted infection were infected with *T vaginalis* only, 79 (9%) participants had *N gonorrhoea*, and 161 (18%) had *C trachomatis*.

Table 1: **Participant characteristics**

	Follow-up intervals for analysis of HIV-1 acquisition by women (N=1314 HIV-1-seronegative women)			Follow-up intervals for analysis of HIV-1 transmission from women to men (N=2476 HIV-1-seropositive women)		
	Any hormonal contraception	No hormonal contraception	p value*	Any hormonal contraception	No hormonal contraception	p value*
Demographic characteristics						
Age of HIV-1 seronegative partner, years	30·0 (26·0–35·4)	30·5 (25·0–37·8)	0·02	34·0 (29·7–39·9)	35·6 (30·0–43·0)	<0·0001
Children within the partnership	2·0 (1·0–3·0)	2·0 (0·0–3·0)	0·9	1·0 (1·0–2·0)	1·0 (0·0–2·0)	0·03
Sexual behaviour, HIV-1-uninfected partner						
Any unprotected sex with study partner, past month	77/896 (8·6%)	460/6125 (7·6%)	0·4	389/3006 (12·9%)	1011/9998 (10·1%)	0·009
Any sex with an outside partner, past month	29/897 (3·2%)	160/6024 (2·7%)	0·5	294/3006 (9·8%)	1221/10 000 (12·2%)	0·01
Medical characteristics						
CD4 count (cells per μL) in the HIV-1 infected partner	402 (286–601)	405 (298–562)	0·7	467 (343–656)	452 (324–631)	0·04
Plasma HIV-1 concentration (log_{10} copies per mL) in the HIV-1-infected partner	4·3 (3·3–4·9)	4·4 (3·6–5·0)	0·2	3·9 (3·2–4·5)	4·0 (3·2–4·7)	0·1
Pregnant, female partner†	47/898 (5·2%)	967/6027 (16·0%)	<0·0001	146/2876 (5·1%)	1288/9675 (13·3%)	<0·0001

Data are n/N (%) or median (IQR). *Comparisons among contraceptive-exposure groups are adjusted for correlation by multiple measures from the same woman with generalised estimating equations. The number of data points assessed for each cell is total number of visits with each covariate characteristic during study follow-up. †Contraceptive use during pregnancy intervals was either contraceptive failures documented at the time of pregnancy detection or contraceptive uptake during the early postpartum period.

Table 2: **Participant characteristics during quarterly follow-up intervals with and without hormonal contraceptive use**

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

For most of the 3790 HIV-1-serodiscordant couples included in the analysis, the HIV-1-infected partner was female (table 1). Most couples were married with children. The median age was in the mid-30s, and 321 (24%) of 1314 uninfected women were younger than 25 years. In HIV-1-seropositive participants, the median CD4 count was 455 cells per μL (IQR 337–626) and median plasma HIV-1 RNA concentration was 4·10 log_{10} copies per mL (IQR 3·37–4·73). More than a quarter of women were pregnant during study follow-up (table 1).

27 couples enrolled in the randomised trial[13] were subsequently reported not to have HSV-2 or HIV-1 infection and were excluded from the analysis, as were 76 couples in which the HIV-1-uninfected participant did not complete any follow-up visits for assessment of HIV-1 seroconversion. For 350 couples (151 with an HIV-1-uninfected woman and 199 with an HIV-1-uninfected man) in which the HIV-1-infected partner started ART, subsequent visits were censored.[18]

At enrolment, 194 (15%) of 1314 HIV-1-seronegative and 430 (17%) of 2476 HIV-1-seropositive women used hormonal contraception; injectable contraception was more commonly used than oral pills (477 [13%] of 3790 women used injectable *vs* 147 [4%] who used oral contraception). 275 (21%) of 1314 HIV-1-seronegative women and 815 (33%) of 2476 HIV-1-seropositive women used hormonal methods during study follow-up. Most women did not switch contraceptive methods during follow-up (1085 [83%] of 1314 HIV-1-seronegative women and 1909 [77%] of 2476 HIV-1-seropositive women). However, among 1321 women who ever used hormonal contraception during the study, 634 (48%; 448 [48%] of 945 HIV-1-seropositive women and 186 [49%] of 376 HIV-1 seronegative women) were not using such methods at some point during follow-up.

Median follow-up for HIV-1-seronegative women was 18·0 (IQR 12·6–24·2) months and for seronegative men was 18·7 months (IQR 12·8–24·2). Retention at 12 months for HIV-1-seronegative women was 93% (1153 of 1238 women) and for seronegative men was 90% (2098 of 2331 men). Retention at 24 months for HIV-1-seronegative women was 87% (423 of 484 women) and for seronegative men was 84% (812 of 970 men). HIV-1-seronegative partners accrued 5157·9 person-years of follow-up for assessment of HIV-1 seroincidence, during which 167 HIV-1 seroconversions occurred. Of the 73 infections in women, 62 (85%) were determined by viral sequencing to be genetically linked within the partnership, and of the 93 infections in men, 59 (63%) were linked.

During follow-up, hormonal contraceptives were used more frequently by couples with young HIV-1-uninfected partners and couples who did not experience pregnancy (table 2). Sexual behaviours did not differ for HIV-1-uninfected women during periods when they were using hormonal contraception compared with when they were not using hormonal contraception. Unprotected sex was more likely and sex with an external partner was less likely for HIV-1-uninfected men, during periods when their female partner was using hormonal contraception than it was when their partner was not taking hormonal contraception. Concentrations of plasma HIV-1 RNA and

	Number of HIV-1 seroconversions/person-years	Incidence per 100 person-years	Unadjusted Cox proportional hazards regression analysis		Adjusted Cox proportional hazards regression analysis*		Adjusted marginal structural models analysis†	
			Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Odds ratio (95% CI)	p value
All women	73·0/1782·8	4·09	..	..	..	..	..	..
No hormonal contraception	60·0/1586·2	3·78	Reference	Reference	Reference	Reference	Reference	Reference
Any hormonal contraception	13·0/196·6	6·61	1·73 (0·95–3·15)	0·07	1·98 (1·06–3·68)	0·03	1·84 (0·98–3·47)	0·06
Injectable	10·0/146·1	6·85	1·80 (0·92–3·52)	0·08	2·05 (1·04–4·04)	0·04	2·19 (1·01–4·74)	0·05
Oral	3·0/50·5	5·94	1·53 (0·48–4·90)	0·47	1·80 (0·55–5·82)	0·33	1·63 (0·47–5·66)	0·44

*Multivariate Cox proportional hazard regression model, adjusted for age, concentrations of plasma HIV-1 in the HIV-1-infected partners, and time varying unprotected sex and pregnancy. Further adjustment for additional factors did not substantially change the findings. †Weighted marginal structural model is adjusted for age, region, number of children, concentration of plasma HIV-1 RNA in the HIV-1-infected partner, and month of visit (5-knot cubic spline with knots at the 5th, 25th, 50th, 75th, and 95th percentiles) and contraceptive history; weights are truncated at the 1st and 99th percentiles.

Table 3: Hormonal contraceptive use and risk of HIV-1 acquisition by women

	Number of genetically linked HIV-1 seroconversions/ person-years	Incidence per 100 person-years	Unadjusted Cox proportional hazards regression analysis		Adjusted Cox proportional hazards regression analysis*		Adjusted marginal structural model analysis†	
			Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Odds ratio (95% CI)	p value
All men	59·0/3375·1	1·75	..	..	..	..	..	..
No hormonal contraception	40·0/2647·9	1·51	Reference	Reference	Reference	Reference	Reference	Reference
Any hormonal contraception	19·0/727·2	2·61	1·76 (1·02–3·05)	0·04	1·97 (1·12–3·45)	0·02	2·05 (1·12–3·74)	0·02
Injectable	15·0/567·3	2·64	1·79 (0·99–3·22)	0·05	1·95 (1·06–3·58)	0·03	3·01 (1·47–6·16)	0·003
Oral	4·0/159·9	2·50	1·70 (0·60–4·81)	0·31	2·09 (0·75–5·84)	0·16	2·35 (0·79–6·95)	0·12

*Multivariate Cox proportional hazard regression model, adjusted for age, plasma HIV-1 levels in the HIV-1 infected partner, and time varying unprotected sex and pregnancy. Further adjustment for additional factors did not substantially change the findings. †Weighted marginal structural model is adjusted for age, region, number of children, plasma HIV-1 RNA concentration in the HIV-1 infected partner, and visit month (5-knot cubic spline with knots at the 5th, 25th, 50th, 75th and 95th percentiles) and contraceptive history; weights are truncated at the 1st and 99th percentiles.

Table 4: Hormonal contraceptive use and risk of HIV-1 transmission from women to men

CD4 counts were similar for hormonal-contraception exposed versus unexposed periods.

Rates of HIV-1 acquisition were higher in women using hormonal contraception than in those who were not (table 3). In multivariate Cox proportional hazards analysis adjusted for age, pregnancy, unprotected sex, and concentrations of plasma HIV-1 in HIV-1-infected partners, use of hormonal contraceptives was associated with a two times increased risk of HIV-1 acquisition (adjusted hazard ratio 1·98, 95% CI 1·06–3·68). Increased risk was reported for both injectable (adjusted hazard ratio 2·05, 95% CI 1·04–4·04) and oral contraceptive use (1·80, 0·55–5·82), although the analysis of oral contraceptive use included only 50·5 person-years and was not statistically significant. The results from the marginal structural models were generally in agreement with the Cox regression models. No evidence showed that the effect of hormonal contraception on HIV-1 risk was different for HSV-2-seronegative women (195 [15%] of 1283) versus seropositive women (adjusted hazard ratio 1·56 *vs* 2·00, $p_{interaction}$=0·82) or for women younger than 25 years (321 [24%] of 1314) versus those 25 years or older (adjusted hazard ratio 1·96 *vs* 2·21, $p_{interaction}$=0·82).

The rate of HIV-1 transmission from women using hormonal contraceptives to their male partners was higher than was the rate of transmission from women who did not use hormonal contraceptives (table 4). In multivariate analysis adjusted for age, pregnancy, unprotected sex, and concentrations of plasma HIV-1 in HIV-1-infected partners, men's HIV-1 risk was increased two times when their partners were using hormonal contraception (adjusted hazard ratio 1·97, 95% CI 1·12–3·45; table 4). Both injectable and oral contraceptive use by female partners were associated with increased HIV-1 risk for men, although the effect was significant only for injectable contraception (table 4). The marginal structural model analyses generated similar results to the Cox proportional hazards regression.

To account for the potential persistent biological effects of hormonal contraception on HIV-1 risk when women switched contraceptive methods, we assessed the effect of extending the exposure window for 3 months after last hormonal contraceptive use (thus, women could be exposed to more than one method during one study visit window). This assessment affected 32·1 (2%) of the 1782·8 person-years and one seroconversion event for the HIV-1 acquisition analysis and 70·9 (2%) of the 3375·1 person-years and one event for the female-to-male transmission analysis. The results of these analyses were not substantially different than those shown in table 3 and table 4 (data not shown). When we limited the analysis of HIV-1 acquisition by women to those 62 outcomes that were genetically linked to their male partners, the effect estimates were not substantially changed (for any

	Detection of any genital HIV-1 RNA					Quantity of genital HIV-1 RNA detected (log_{10} copies/swab)				
	n/N (%)	Odds ratio (95% CI)	p value	Adjusted odds ratio* (95% CI)	p value	Median (IQR)	Regression coefficient* (95% CI)	p value	Adjusted regression coefficient† (95% CI)	p value
Overall	1011/1691 (59·9)	..	..	..	..	3·18 (2·08 to 3·85)	..	..	..	..
No hormonal contraception	782/1333 (58·7)	Reference	Reference	Reference	Reference	3·14 (2·08 to 3·91)	Reference	Reference	Reference	Reference
Any hormonal contraception	230/358 (64·3)	1·27 (0·99 to 1·61)	0·06	1·51 (1·13 to 2·01)	0·0054	3·29 (2·08 to 3·91)	0·10 (−0·01 to 0·21)	0·08	0·14 (0·04 to 0·23)	0·0055
Injectable	180/272 (66·2)	1·38 (1·05 to 1·81)	0·05	1·67 (1·21 to 2·31)	0·02	3·38 (2·08 to 4·02)	0·15 (0·03 to 0·28)	0·02	0·19 (0·08 to 0·30)	0·0005
Oral	50/86 (58·1)	0·98 (0·63 to 1·52)	0·43	1·06 (0·62 to 1·84)	0·49	2·96 (2·08 to 3·65)	−0·07 (−0·28 to 0·14)	0·53	−0·05 (−0·24 to 0·14)	0·60

*Average difference in HIV-1 RNA concentration. †Adjusted for concentration of plasma HIV-1 RNA and CD4 count.

Table 5: Endocervical concentrations of HIV-1 RNA in HIV-1 seropositive women, by contraceptive method

hormonal contraceptive use, Cox regression adjusted hazard ratio 2·06, 95% CI 1·05–4·03 and marginal structural model odds ratio 2·01, 95% CI 1·02–3·95). In a third sensitivity analysis, we censored observations during pregnancy and adjusted our Cox model for age, unprotected sex, and concentrations of plasma HIV-1 in HIV-1-infected partners. We did not see substantial differences in the effect estimates (Cox regression adjusted hazard ratio 1·84, 95% CI 0·97–3·49, for the association of hormonal contraception and HIV-1 acquisition among women and 1·86, 1·04–3·32, for the association of hormonal contraception and HIV-1 transmission to men) for this approach compared with our primary study models.

We measured endocervical concentrations of HIV-1 RNA from a single timepoint in 1691 HIV-1-infected women (table 5). Women using injectable contraception at the time of endocervical-sample collection were more likely to have genital HIV-1 RNA detected than were those not using hormonal contraception. Concentrations of genital HIV-1 RNA were also higher in those using injectable contraception than in those not using hormonal contraception, by an average of 0·19 log_{10} copies per swab, after adjustment for plasma HIV-1 concentrations and CD4 cell count (table 5). No association was identified between contraception and concentrations of plasma HIV-1 RNA collected at the same time as endocervical samples (median 3·91 log_{10} copies per mL [IQR 3·07–4·50] for injectable users *vs* 4·03 log_{10} copies per mL [IQR 3·22–4·65] for non-users; p=0·10), suggesting a localised effect of hormonal contraception on increased concentrations of HIV-1 in the female genital tract.

Discussion

Use of hormonal contraceptives was associated with a two-times increase in the risk of HIV-1 acquisition by women and HIV-1 transmission from women to men. Injectable methods were the most common form of hormonal contraception used by our study population and subgroup analyses showed significantly increased HIV-1 risk associated with injectable use. Few women used oral contraceptives in our study; oral contraceptive use was associated with a non-significant increase in HIV-1 risk and our results are insufficient for drawing definitive conclusions about oral contraceptive use and HIV-1 risk. Our results were robust when we adjusted for multiple potential confounding factors, undertook different analytical approaches, and did sensitivity analyses.

Previous studies of HIV-1-acquisition risk related to contraceptive use have had inconsistent results, partly because of variable methodological quality.[9] As a result, public health policies—targeted risk-reduction counselling and strategies to promote alternative contraceptive methods for women with or at risk of HIV-1—have not been implemented. Our findings provide new data that show that contraception might increase a woman's risk of acquiring HIV-1, and they are consistent with longitudinal studies of sex workers in Kenya and family planning attendees from Uganda and Zimbabwe.[7,24] Moreover, to our knowledge, ours is the first prospective study to show increased HIV-1 risk in male partners of HIV-1-infected women using hormonal contraception. We noted raised concentrations of HIV-1 RNA in endocervical secretions from HIV-1-infected women using injectable methods, suggesting a potential mechanism for increased risk of HIV-1 transmission. Studies of HIV-1 transmission from women to men are urgently needed to confirm or refute our findings.

Hormonal contraceptives might have physiological actions beyond pregnancy prevention, including possible risks of bone-density loss, cervical cancer, and *Chlamydia trachomatis*.[28–30] Clinical and laboratory studies have suggested possible mechanisms by which hormonal contraception could influence HIV-1 susceptibility and infectiousness including changes to vaginal structure, cytokine regulation, CCR5 expression, and cervicovaginal HIV-1 shedding.[31]

Our analyses controlled for age, pregnancy, condom use, and HIV-1 concentrations in the infected partner; controlling for additional demographic, clinical, and behavioural factors did not alter our results. Only a clinical trial with random assignment of women to effective hormonal contraception versus non-hormonal contraception could definitively assess HIV-1 risk from

Panel: Research in context

Systematic review

We searched PubMed up to July, 2011, to identify studies relating use of hormonal contraceptives to HIV-1 risk, with the search terms "hormonal contraception", "hormonal contraceptive", "HIV-1", and "HIV-1 acquisition or transmission" in different combinations. Additionally, systematic reviews and one meta-analysis published on this topic were reviewed.

Interpretation

Several studies show—with similar magnitude of their effect estimates—the potential for hormonal contraception to increase women's risk for acquiring HIV-1, even after controlling for sexual behaviour. Our study is the first with adequate power to assess and show the potential for hormonal contraceptive use by HIV-1-seropositive women to increase risk of transmitting the virus to their male partners. These findings have important implications for family planning and HIV-1-prevention programmes, especially in settings with high HIV-1 prevalence.

different contraceptive methods with certainty that bias in contraceptive choice and bias due to unmeasured confounding did not influence the results. Such a study might be difficult to implement because of women's preferences for different contraceptive methods and the likelihood of contraceptive switching that could undermine randomisation.

Limitations of our study were that contraceptive use was determined by self-report—we did not gather data on adherence to contraception, and we did not record the specific brand of contraception and thus cannot comment on HIV-1 risks from specific exogenous hormones. During the study period, low-dose combination hormonal oral contraceptives and long-acting injectable depot medroxyprogesterone acetate (DMPA) were the most commonly used methods in national family planning programmes; few studies have assessed HIV-1 risk from other injectable methods (eg, norethisterone enanthate).[12] Most participants in our study were participating in an HIV-1-prevention randomised trial and were recruited broadly from HIV-1 testing and care centres. Nearly all HIV-1-infected partners were co-infected with HSV-2; however, HSV-2 seroprevalence is more than 80% in HIV-1-infected people in sub-Saharan Africa.[32] Thus, these factors are unlikely to limit the generality of our findings. We censored follow-up for those couples in which the HIV-1-infected partner initiated ART. Future studies with long post-ART follow-up should assess whether increased risk of HIV-1 acquisition and transmission occurs in the context of ART use.

Several observational studies have shown increased HIV-1 risk for women using hormonal contraceptives;[7,24] our findings suggest that male partners of HIV-1-infected women using hormonal contraception also face heightened HIV-1 risk. The benefits of effective hormonal contraceptive methods are unequivocal and must be balanced with the risk for HIV-1 infection. Our findings argue for policies to counsel women about the potential for increased HIV-1 risk with hormonal contraceptive use, especially injectable DMPA use, and the importance of dual protection with condoms to decrease HIV-1 risk (panel).

Our data do not provide estimates of HIV-1 risk related to other hormonal contraceptives, such as implants, patches, or combination injectables. Data on HIV-1 risk associated with these methods and non-hormonal contraceptive methods, such as intrauterine devices, are urgently needed, and strategies to improve the accessibility and uptake of these lower-dose and non-hormonal methods should be prioritised. Contraceptive counselling should be combined with HIV-1 counselling and testing, with joint scale-up of both approaches essential for optimisation of reproductive health and HIV-1-prevention choices for women and couples. Additionally, as national HIV-1-prevention programmes begin to incorporate antiretroviral pre-exposure prophylaxis,[33–35] this new HIV-1-prevention method could be offered to women using contraceptives or their partners.

Contributors

RH, DD, and JMB designed the study and RH and DD did the analysis. RH and JMB wrote the initial draft. All authors contributed to the data collection and writing of the report and approved the final draft.

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Conflicts of interest

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